UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/206,132	12/07/1998	GORDON J. FREEMAN	RPI-008CPDV	5096

959 7590 01/29/2003

LAHIVE & COCKFIELD
28 STATE STREET
BOSTON, MA 02109

EXAMINER	
NGUYEN, QUANG	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 01/29/2003

21

Please find below and/or attached an Office communication concerning this application or proceeding.

Offic Action Summary	Application No. 09/206,132	Applicant(s) FREEMAN ET AL.	
	Examiner Quang Nguyen, Ph.D.	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover she t with the correspond nce address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 August 2002 and 13 November 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *62,63,71-74,76-86 and 88-112* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *95-98* is/are allowed.

6)☒ Claim(s) *62,63,71-74,76-86,88-94 and 99* is/are rejected.

7)☒ Claim(s) *100-105 and 107-112* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants' amendments filed on 08/21/02 and 11/13/02 in Papers No. 19 and 20 have been entered.

Amended claims 62-63, 71-74, 76-86, 88-94 and new claims 95-112 are pending in the present application, and they are examined on the merits herein.

The text of those sections of Title 35 U.S.C. Code not included in this action can be found in a prior Office Action.

Claim Objections

Claims 81 and 106 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of previous claims 73 and 99, respectively. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. This is because the transfection of a nucleic acid molecule encoding a B7-2 molecule in a tumor cell or cells of a solid tumor *in vivo* has no effect on the inhibition of the invariant chain expression. Therefore, there is no nexus between the transfection of a nucleic acid molecule encoding a B7-2 molecule in a tumor cell or cells of a solid tumor *in vivo* and the inhibition of the invariant chain expression in said tumor cell or said cells of a solid tumor *in vivo*.

Claim Rejections - 35 USC § 112

Amended claims 62-63, 71-74, 76-86, 88 and 90-94 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a

method for treating a mammalian subject having **a solid tumor**, comprising **direct injection** into cells of said tumor a nucleic acid encoding B7-2 molecule in a form suitable for expression of the B7.2 molecule in cells of said tumor and wherein **said B7.2 molecule has the ability to costimulate a T cell and the ability to bind a CD28 or CTLA4 ligand** such that the growth of said tumor is inhibited; the same method for modifying a tumor cell *in vivo*, does not reasonably provide enablement for a method of treating a subject with any tumor or a method of modifying any tumor cell *in vivo* to express a B7-2 molecule by transfecting cells of the tumor or the tumor cell with a nucleic acid molecule encoding B7.2 by any route of delivery. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims for the same reasons stated in the previous Office Action.

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

Claims 62-63, 71-72, 88 and 90-94 are drawn to a method for treating a subject with a tumor comprising modifying cells of the tumor *in vivo* to express a T cell costimulatory molecule, B7-2, to thereby treat the subject, wherein cells of the tumor are

modified in vivo by delivering to the cells in vivo a nucleic acid molecule encoding B7-2 in a form suitable for expression of B7-2 by the cells.

Claims 73-74 and 76-86 are drawn to a method of modifying a tumor cell to express a B7-2 molecule comprising transfecting a tumor cell with a nucleic acid molecule encoding a B7-2 molecule such that B7-2 is expressed by the tumor cell. It should be noted that these claims also encompass an *in vivo* method of modifying a tumor cell.

With regard to the elected invention, the instant specification discloses that tumor cells could be modified *in vivo* by introducing a nucleic acid molecule encoding B7-2 into the tumor cells for expression of the co-stimulatory molecule on the surface of tumor cells. Similarly, nucleic acid molecules encoding MHC class I or class II molecule or an antisense sequence of a MHC class II associated protein or the invariant chain gene (Ii gene) could also be introduced into tumor cells *in vivo* (See specification, pages 18-19). Example 5 shows that no tumor growth was observed upon intradermal or subdermal implantation of J558 plasmacytoma cells transfected *in vitro* with an expression vector containing cDNA encoding either mouse B7-2 or B7-1 molecule in syngeneic Balb/c mice. The above evidence has been noted and considered. However, the evidence is not reasonably extrapolated to the instant broadly claimed invention for the reasons discussed below.

(a) The breadth of the claims. The instant claims encompass a method for treating a subject with a tumor and modifying a tumor cell to express a B7-2 molecule comprising transfecting or delivering to the tumor cell or cells of the tumor with a nucleic

acid molecule encoding B7-2 by any route of administration. Additionally, the claims encompass any types of tumor *in vivo* including a solid tumor as well as a non-solid tumor such as lymphoma and leukemia.

(b) State of the art and the unpredictability of the art. The nature of the instant claims falls within the realm of gene therapy, specifically *in vivo* gene therapy. At the effective filing date of the present application, the art of gene therapy was immature and highly unpredictable. In reviewing the state of the gene therapy art at about the time of the instant invention, Marshall (Science 269:1050-1055, 1995) stated that "there has been no unambiguous evidence that genetic treatment has produced therapeutic benefits" (page 1050, column 1, lines 5-9 of the last paragraph) and that "with more than 100 clinical trials started and hundreds of millions of dollars at stake, the field is struggling to meet expectations" (page 1050, subtitle). In the same review article, NIH director Harold Varmus was quoted as saying "Despite the growing support for gene therapy, the field remains at a very early stage of development. While there are several reports of convincing gene transfer and expression, there is still little or no evidence of therapeutic benefit in patients – or even in animal models" (page 1050, column 2, first full paragraph). Even in a meeting review article on gene therapy and translational cancer research many years after the effective filing date of the present application, Dang et al. (Clin. Cancer Res. 5:471-474, 1999) stated that "This workshop reviewed some recent advances in gene delivery, gene expression, immune manipulation, and the development of molecular targets and stressed that all of these fields will need further advancement **to make gene therapy a reality**" (page 471,

column 1, last sentence of first paragraph). Thus, it is clear that the art of gene therapy at the effective filing date of the instant invention (at least to 11/03/1993) was still immature, unpredictable and that the obstacles associated with gene therapy for achieving therapeutic effects could not have been overcome with routine experimentation.

Furthermore, at the effective filing date of the present application, *in vivo* vector targeting to desired cells, tissues or organs, for this instance tumor cells, continues to be unpredictable and inefficient. This is supported by numerous teachings available in the art, including those published several years after the effective filing date of the present application. For examples, Miller & Vile (FASEB 9:190-199, 1995) reviewed the types of vectors available for *in vivo* gene therapy, and concluded that ""for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances .... Targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1). Deonarain (Exp. Opin. Ther. Patents8:53-69, 1998) reviewed new techniques for gene delivery under experimentation in the art which show promise, but they are currently even less efficient than the viral gene delivery (see page 65, first paragraph under Conclusion section). Verma & Somia (Nature 389:239-242,1997) also reviewed various vectors known in the art for use in gene therapy and the problems which are associated with each and clearly indicated that even several years after the effective filing date of the present application, resolution to vector targeting had not been achieved in the art (see the entire article).

Verma & Somia discussed the role of the immune system in inhibiting an efficient targeting of viral vectors such that an efficient transgene delivery and expression in target cells could not be achieved (see page 239, and second and third columns of page 242).

(c) The amount of direction or guidance presented. As the term "treating" encompasses various embodiments including the inhibition to eradication of a tumor growth, preventing or inhibiting a tumor metastasis or inhibiting the recurrence of a tumor, the instant specification is not enabled for such a broadly claimed invention. Apart from the exemplification showing that transfected J558 cells expressing B7-2 were unable to grow in naïve mice even after three weeks of intradermal or subdermal implantations, the specification does not provide sufficient guidance for a skilled artisan on how to achieve the full breadth of therapeutic effects contemplated by Applicants, particularly in light of the state of the gene therapy art discussed above. It is further noted that Colombo et al. (Cancer Immunol. Immunother 41:265-270, 1995) state that "It is clear that tumor inhibition and/or the induction of systemic immunity are not by themselves sufficient for evaluation of treatment efficacy and curative potential" (page 268, column 1, middle paragraph). This is because tumor inhibition has been studied by injecting tumor cell suspensions, and it is widely known in the art that tumor stroma plays an important role in tumor uptake, growth and progression; and therefore this situation differs from an established tumor nodules in a subject having a tumor. Colombo et al. further noted that the induction of systemic immunity with activation of cytotoxic T lymphocytes (CTL) might not be sufficient to destroy existing tumor cells

growing in their own stroma for the various factors among which are the loss of MHC class I antigens by tumor cells and the impaired migration of CTL at the tumor site (page 268, column 1, second full paragraph). Furthermore, one of the Applicants (Dr. Lee Nadler) also raised a concern that T cells become tolerant of normally developing tumors, and as such costimulation could prove ineffective (Travis, Science 259:310-311, 1993; page 311, middle column). There is no evidence of record indicating or suggesting that the tolerance or anergy of T cells in a subject having a naturally occurring tumor has been overcome so that the breadth of therapeutic results contemplated by Applicants could be attained without undue experimentation. The physiological art is also recognized as unpredictable (MPEP 2164.03). As set forth in *In re Fisher*, 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> That scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the are; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

Additionally, the Appeal courts have also stated that reasonable correlation must exist between scope of exclusive right to patent application and scope of enablement set forth in the patent application (27 USPQ2d 1662 *Ex parte Maizel.*).

As the instant claims encompass any route of delivering a nucleic acid molecule encoding a B7-2 molecule alone or in combinations with a nucleic acid molecule encoding a B7 protein, a MHC class I or class II molecule, or an antisense sequence of the invariant chain gene into a subject having a tumor for treating or modifying tumor

cells. The instant specification fails to teach a skilled artisan on how to overcome the unpredictability for vector targeting *in vivo* known in the art (as already discussed above) such that an efficient gene transfer and expression of encoded molecules such as B7-2 protein, B7 protein, MHC class I or class II molecule, or an antisense sequence of the invariant chain gene could be achieved in tumor cells of a subject by any mode of delivery to attain the desired anti-tumor responses. In the absence of such teachings provided by the instant specification, coupled with the lack of guidance provided by the prior art at the effective filing date of the present application on this issue, it would have required undue experimentation for one skilled in the art to make and use the instant broadly claimed invention.

With respect to claims encompassing modifying cells of non-solid tumors such as lymphoma and leukemia *in vivo*, the present specification offers no guidance for a skilled artisan on how to deliver an effective amount of a nucleic acid encoding B7-2 molecule into a sufficient amount of lymphoma or leukemia cells by any route of delivery such that a critical level of transfected cells could be attained to induce the desired anti-tumor effects. There are several obstacles to this application, some of which are already discussed briefly above. These include the adverse host immune reactions against the nucleic acid molecules encoding B7-2 to inhibit an effective level of said nucleic acid molecules to the desired cells, the dilution effect of the delivered nucleic acid molecules due to the circulation of lymphoma or leukemia cells in the blood system, and unlike localized solid tumors the T cell repertoire of the subject may already well be exposed to tumor antigens of lymphoma or leukemia and become anergized

and as a result, costimulation with tumor cells expressing B7-2 could prove ineffective. It should be stressed that only tumor cells expressing an effective level of B7-2 could induce a T cell anti-tumor response. This is supported by the teachings of Lenschow et al. (Proc. Natl. Acad. Sci. 90:11054-11058, 1993) showing that B7-2 is naturally present on antigen presenting cells such as dendritic cells and B cells, and therefore it is reasonable to assume that B lymphoma cells could naturally express some level of B7-2, but presumably at a level too low to induce any effective T cell anti-tumor response. With the lack of sufficient guidance provided by the instant disclosure, particularly the lack of any example showing that an effective expression level of B7-2 could be attained in transfected lymphoma or leukemia cells *in vivo* to induce an effective T cell anti-tumor response to yield the desired results contemplated by Applicants, it would have required undue experimentation for a skilled artisan to make and use the full scope of the methods as claimed.

(d) The relative skill of those in the art. Although the relative skill of an artisan in the art of molecular biology and immunology was high, the attainment of therapeutic effects, particular the broad range of therapeutic effects contemplated by Applicants, via gene therapy and *in vivo* vector targeting remains unpredictable even many years after the effective filing date of the present application, coupled with the lack of sufficient guidance provided by this disclosure, it would have required undue experimentation for a skilled artisan to make and use the methods as claimed.

Accordingly, due to the lack of sufficient guidance provided by the specification regarding to the issues raised above, the unpredictability of the gene therapy art, and

the breadth of the claims, it would have required undue experimentation for one skilled in the art to make and use the instant broadly claimed invention.

Response to Arguments

Applicants' arguments related to the above rejection in the Amendment filed on 08/21/02 in Paper No. 19 (pages 9-15 and 18) have been fully considered.

With respect to the issue of any route of administration, Applicants basically presented the same arguments such as the instant invention does not require long-term transgene expression or widespread delivery to target tumor cells, and the presently claimed invention only requires a subset of tumor cells to transiently express B7-2 to yield a desired therapeutic effect, and that the anti-tumor immune response induced by the modified tumor cells is effective against both the modified tumor cells and unmodified tumor cells which do not express the costimulatory molecule. Additionally, Applicants argue that the Examiner has presented no evidence indicating that Applicants' method fails to produce a level of B7-2 to achieve at least modest therapeutic effect. Examiner respectfully finds Applicants' arguments to be unpersuasive for the same reasons presented in the previous Office Action, and they are summarized as below.

Although the examiner agrees with Applicants that long-term transgene expression and wide-spread transgene expression in target tumor cells may not be required for the presently claimed invention, a critical amount of target tumor cells expressing an effective level of B7-2 molecule is essential to generate an effective T cell

anti-tumor response to yield the desired therapeutic effects. The instant specification offers no guidance on any conditions or any working example showing that the critical amount of target tumor cells expressing an effective level of B7-2 could be achieved through *in vivo* gene therapy by any route of delivery. Moreover, even several years after the effective filing date of the present application, *in vivo* vector targeting to desired cells remains unpredictable, and therefore therapeutic effects obtained through an effective transgene delivery and expression in target cells also remain unpredictable as evidenced by the teachings of Miller et al., Deonarain, Verma et al. Given the lack of sufficient and specific guidance provided by the present disclosure, it would have required undue experimentation for a skilled artisan to make and use the instant broadly claimed invention. Moreover, Applicants' arguments do not provide any factual evidence indicating or suggesting that obstacles associated with *in vivo* vector targeting have been overcome at the effective filing date of the present application such that induction of an effective T cell anti-tumor response could be obtained *in vivo* by administering a nucleic acid molecule encoding B7-2 to a tumor cell by any route of delivery. In light of the totality of the prior art as a whole, as well as taken the Wands factor into consideration as discussed in the above rejection, it is Applicants' burden to provide evidence indicating that Applicants' method could produce a level of B7-2 to achieve at least modest therapeutic effects via gene therapy by any route of delivery.

With respect to the disclosure of Colombo et al., Applicants argue basically that the tumor cell types and method of introduction into an animal in the Colombo reference are not the same as used in Applicants' experiments (e.g., tumor celll suspensions of

J558 plasmacytoma cells transfected to express B7-2 implanted intradermally or subdermally into Balb/c mice) and therefore the comments of Colombo et al. with respect to tumor growth are not relevant to the present invention. Applicants' arguments are respectfully found to be unpersuasive. Firstly, the claims are not limited to any specific tumor cell type, nor does the example 5 of the present invention reflect the *in vivo* gene immunotherapy of the methods as claimed. Secondly, the main issue of the cited Colombo reference is that the tumor stroma plays an important role in tumor uptake, growth and progression, and that tumor inhibition studied by injecting tumor cell suspensions is not sufficient for evaluation of treatment efficacy and curative potential. Thirdly, because no tumor growth was observed after three weeks of implanting a suspension of J558 cells transfected with a nucleic acid encoding B7.2 molecule into a naïve syngeneic Balb/c mice means that Applicants have attained a broad range of therapeutic effects encompassing curing or eradicating any tumor in a cancer patient for the methods as claimed. Furthermore, Applicants have not provided any factual evidence indicating that the broad range of contemplated therapeutic results has been obtained.

With respect to the quote of Dr. Lee Nadler, Applicants argue that Examiner overstates the comments of Dr. Nadler, and Applicants assert that the existence of immuno-tolerance to tumors is highly speculative and is refuted by the presence of antibodies to the tumor antigens, and that the majority of subjects with tumors do not develop tolerance to the tumors, but rather merely mount unsuccessful immune responses. Applicants' arguments are respectfully found to be unpersuasive because

the mere presence of antibodies to the tumor antigens does not indicate in any manner that T cells do not become tolerant of normally developing tumors in patients, and this is probably the main reason why unsuccessful immune responses were observed in the majority of subjects with tumors. The Examiner already cited the comments of Dr. Nadler who raised the possibility of the existence of T cell immunotolerance to normally developing tumors in patients, it is Applicants' burden to provide factual evidence to refute this possibility, and not the Examiner. Furthermore, there is no evidence of record indicating that Applicants have achieved any cure or preventing the recurrence of any normally developing tumor (encompassing within the scope of treating) in a patient by the methods as claimed.

With respect to the issue of non-solid tumors, Applicants basically argue that the Lenchow article investigates the expression of B7-2 on normal B cells and does not teach or suggest that B lymphoma cells normally express some level of B7-2 at a level to low to induce any effective T cell anti-tumor response. Applicants' argument is found unpersuasive because Applicants still have not provide any objective evidence showing various obstacles such as the adverse host immune response reactions, the dilution effect of the delivered nucleic acid molecules have been overcome such that an effective amount of a nucleic acid encoding B7-2 molecule could be delivered by any route of delivery into a sufficient amount of lymphoma or leukemia cells to obtain a critical level of transfected cells to induce the desired anti-tumor effects. Since B7-2 is naturally present on antigen presenting cells such as dendritic cells and B cells, and therefore it is reasonable to assume that B lymphoma cells could naturally express

some level of B7-2, but presumably at a level too low to induce any effective T cell anti-tumor response. Applicants have not provided any objective evidence to refute this reasonable assumption.

Accordingly, amended claims 62-63, 71-74, 76-86, 88 and 90-94 remain rejected under 35 U.S.C. 112, first paragraph, for the reasons set forth above.

Following is a new ground of rejection necessitated by Applicants' amendment to claim 89.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 73, 81, 89, 99 and 106 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is unclear what is encompassed by the method recited in claim 81 and new claim 106. There are no essential steps or critical agents recited for modifying a tumor cell or cells of a solid tumor *in vivo* in inhibiting the expression of the invariant chain. The transfection of a nucleic acid molecule encoding a B7-2 molecule in a tumor cell or cells of a solid tumor *in vivo* in claims 73 and 99, respectively, has no effect on inhibiting the expression of the invariant chain. The metes and bounds of the claims are not clearly determined. Examiner notes that this is the same ground of rejection already set forth in the previous Office Action, and Applicants have not addressed this issue.

Amended claim 89 recites the limitation "wherein local administration is via injection of the nucleic acid molecule into the tumor" in lines 3-4 of the claim. There is insufficient antecedent basis for this limitation in the claim. Which nucleic acid molecule? The metes and bounds of the claim are not clearly determined.

Examiner notes that Applicants have not argued specifically to the rejection of claim 81 made in the previous Office Action in the Amendment filed on 08/21/02 in Paper No. 19.

Conclusions

Claims 95-98 are allowed. Claims 100-105 and 107-112 are objected because they are dependent on the rejected claim 99, and that they would be allowable if they are rewritten in independent formats.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, David Guzo, Ph.D., may be reached at (703) 308-1906, or SPE, Irem Yucel, Ph.D., at (703) 305-1998.

Quang Nguyen, Ph.D.

DAVID GUZO
PRIMARY EXAMINER